IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

NOVOZYMES A/S,	)	
	)	
Plaintiff,	)	
	)	
v.	)	Civil Action No. 05-160-KAJ
	)	
GENENCOR INTERNATIONAL, INC. and ENZYME DEVELOPMENT CORPORATION,	)	
	)	
Defendants.	)	

FINDINGS OF FACT AND CONCLUSIONS OF LAW

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JORDAN, District Judge

I. INTRODUCTION

This is a patent infringement case. Novozymes A/S ("Novozymes") has sued Genencor International, Inc. ("Genencor") and Enzyme Development Corporation ("EDC") (collectively "Defendants"), alleging infringement of U.S. Patent No. 6,867,031 (issued Mar. 15, 2005) (the "'031 patent"). Trial of this matter has been bifurcated: a bench trial on patent infringement, invalidity, and unenforceability was held from March 6 to March 9, 2006, and a second bench trial on willfulness and damages is scheduled to begin on October 10, 2006. The following, issued pursuant to Federal Rule of Civil Procedure 52(a), are my findings of fact and conclusions of law as to the liability issues tried last March.

For the reasons that follow, including my decision on claim construction, I conclude that Defendants have infringed claims 1, 3, and 5 of the '031 patent, that those claims are valid, and that the '031 patent is enforceable. Accordingly, this case will proceed to the second phase trial to decide the issues of willfulness and damages.

II. FINDINGS OF FACT[1]

A. *The Parties*

1. Novozymes is a Danish corporation with a place of business in Bagsvaerd, Denmark. (Uncontested Facts, Docket Item ["D.I."] 101 at ¶ III.A.)

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[1]Throughout these Findings of Fact and Conclusions of Law, I may have adopted without attribution language suggested by one side or the other in this dispute. In all such instances, the finding or conclusion in question has become my own, based upon my review of the evidence and the law. To the extent that any of my findings of fact may be considered conclusions of law or vice versa, they are to be considered as such.

Novozymes is the sole assignee of the '031 patent titled "Amylase Variants." ('031 patent.)

2. Genencor is a Delaware corporation having a principal place of business in Palo Alto, California. (Uncontested Facts, D.I. 101 at ¶ III.B.) Genencor sells an alpha-amylase product under the brand name Spezyme® Ethyl. (*Id.* at ¶ III.V.)

3. EDC is a Delaware corporation having a principal place of business in New York, New York. (*Id.* at ¶ III.C.) EDC is a United States distributor of Genencor's Spezyme Ethyl. (*Id.* at ¶ III.W.)

B. *Technological Background*

1. *Alpha-Amylases*

4. The '031 patent relates to alpha-amylase enzymes. ('031 patent, 1:21-22.) Enzymes are catalysts, meaning that they increase the rate of chemical reactions. (Uncontested Facts, D.I. 101 at ¶ III.E; Arnold,[2] D.I. 120, Trial Transcript ["Tr."] at 143:15-144:1.) The alpha-amylase enzymes described by the '031 patent are proteins (Arnold, Tr. at 139:4-6) that catalyze the breakdown of alpha-1,4-glucosidic bonds (Uncontested Facts, D.I. 101 at ¶ III.F). Alpha-1,4-glucosidic bonds connect individual glucose molecules together to form starch molecules. (*Id.*) By breaking those bonds, alpha-amylases "break apart the starch complexes and convert complex starch into smaller, simpler groups of glucose molecules . . . ." (*Id.*)

5. "[A]lpha-amylases are useful in a variety of commercial applications that involve the processing of starches [,including] . . . the fuel ethanol industry, where

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[2]Dr. Frances Hamilton Arnold is a Professor of Chemical Engineering and Biochemistry at the California Institute of Technology. (Tr. at 131:23-25.)

ethanol fuel is produced from starch-rich crops such as corn, barley, and wheat." (*Id.* at ¶ III.G.) "Alpha-amylases are used in the fuel ethanol industry to liquefy and reduce the viscosity of starch feedstocks so that they are easier to process in the manufacturing plant." (*Id.* at ¶ III.H.)

6. In the process of fuel ethanol production, alpha-amylases are typically added to a starch slurry that is subjected to temperatures above 100°C for up to ten minutes, followed by an incubation at 80°C for a few hours. (Borchert,[3] Tr. at 25:8-15.) Hence, the thermostability of the enzyme, its capacity to withstand high temperatures, is important to its effectiveness in industrial applications. (*See id.* at 25:19-26:4.) By using alpha-amylases with better thermostability, manufacturers can use less of the enzyme and reduce costs. (*Id.* at 26:5-9, 29:12-20.)

7. One way to improve the thermostability of alpha-amylases is to add high levels of calcium to the starch slurry. (*Id.* at 26:15-22.) But high calcium levels interfere with later processing, so that the calcium has to be removed, an additional step that is inconvenient and increases costs. (*Id.* at 26:25-27:14, 29:18-20.)

8. The '031 patent is directed at alpha-amylases, produced by protein engineering, that are thermostable in industrial applications, without the need for added calcium. (*Id.* at 26:5-11; *see generally* '031 patent, 9:48-11:65.)

2. *Protein Engineering*

9. Like all proteins, alpha-amylases are polymers composed of amino acids linked together by peptide bonds into a linear chain. (Uncontested Facts, D.I. 101 at ¶

[3]Dr. Torben V. Borchert is a director of protein design and optimization at Novozymes (Tr. at 16:1-3) and one of the named inventors of the '031 patent.

III.I.) Each protein chain includes many amino acids assembled in a particular order, so that a particular protein may be identified by its ordered sequence of amino acids. (*Id.*) That ordered sequence is referred to as the protein's "amino acid sequence" or its "primary structure." (*Id.*)

10. "One end of a protein chain of amino acids is called the 'N-terminus,' and the other end is called the 'C-terminus.'" (*Id.* at ¶ III.J.) Scientists write an amino acid sequence by listing the amino acids in order from the N-terminus to the C-terminus, using one-letter codes for each of the twenty naturally occurring amino acids. (*Id.* at ¶ III.K.) For example, the amino acid alanine has the one-letter code "A", and asparagine has the one-letter code "N". ('031 patent, 6:44-47.) Protein sequences written using the one-letter codes are disclosed in the '031 patent. (*Id.* at Fig. 1.)

11. "It can be informative when comparing proteins to compare their respective amino acid sequences." (Uncontested Facts, D.I. 101 at ¶ III.N.) The amino acid sequences are typically "aligned" with one another to achieve a visual correspondence of individual amino acids or groups of amino acids that are common to the proteins being compared. (*Id.*) Once sequences are aligned, the percentage of identical amino acid matches in the aligned proteins can be calculated and reported as a percent of "identity," also referred to at times as "homology." (*Id.* at ¶ III.O.) Generally, the alignments and calculations may be done using computer software. ('031 patent, 4:36-45; Devereux,[4] Tr. at 103:20-104:4, 106:11-107:2 (briefly describing the use of software to align protein sequences).)

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[4]Dr. John Rickert Devereux was formerly the president and chief scientific officer of Genetics Computer Group, Inc. (Tr. at 100:16-22.)

12. The function of a protein and the conditions under which it can perform that function are determined at least in part by the protein's amino acid sequence. (Uncontested Facts, D.I. 101 at ¶ III.M.) That is because a particular linear chain of amino acids will fold into a characteristic three-dimensional structure. (Borchert, Tr. at 21:1-7.) The so-called "tertiary" structure of a protein describes the relative positions in three-dimensional space of the protein's atoms. (Machius,[5] Tr. at 456:13-19.) That tertiary structure is the specific overall shape of the protein (*id.* at 456:13-15), which determines the protein's function (*id.* at 457:15-22).[6]

13. Because of the relationship between protein sequence, structure, and function, one can alter the function or other properties of a protein by altering its sequence. Protein engineering is "the deliberate modification of the amino acid sequence of [a] protein," so that the protein's properties can be studied or improved. (Arnold, Tr. at 135:16-21.) Protein sequences can be modified by making substitutions, insertions, or deletions of amino acids in the sequence. (Borchert, Tr. at 23:12-13.)

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[5]Dr. Mischa Machius is an Associate Professor of Biochemistry and Director of the Structural Biology Laboratory at the University of Texas, Southwestern Medical Center (Tr. at 448:17-21), as well as one of the authors of a reference that was much discussed at trial (*see infra* Section II.D).

[6]Proteins are also characterized by their secondary structural elements, which are localized structures, such as alpha helices, beta strands, and loops, that form within the overall tertiary structure. (Machius, Tr. at 456:1-10.) The tertiary structure shows how the secondary structures come together in three dimensions to form the overall shape of the protein molecule. (*Id.* at 456:13-15.) Recall that the primary structure is the amino acid sequence. (*Supra* Finding of Fact ["FF"] ¶ 9.)

14. Protein engineers modify a protein sequence by changing the DNA sequence of the gene that encodes that protein. (Alber,[7] Tr. at 202:23-203:11; Arnold, Tr. at 139:21-140:5.) Each amino acid in a protein sequence corresponds to a triplet of nucleotides in the DNA sequence of the corresponding gene. (Alber, Tr. at 202:25-203:3.) The DNA sequence may be modified "very precisely" (*id.* at 203:5-6), thus allowing the modification of protein sequences.

3. *Claims of the '031 Patent*

15. Novozymes is asserting claims 1, 3, and 5 of the '031 patent. (*See, e.g.,* D.I. 118 at 22-26.) Those claims relate to alpha-amylases originally found in a species of bacteria named *Bacillus stearothermophilus*[8] but then engineered for improved thermostability. ('031 patent, 65:11-17, 65:21-66:12, 66:16-19.)

16. Specifically, claims 1, 3, and 5 relate to alpha-amylases that have two particular amino acids deleted, those at positions 179 and 180, using the numbering of a reference *Bacillus stearothermophilus* alpha-amylase sequence given in the patent, "SEQ ID NO:3." ('031 patent, 65:11-17, 65:21-66:12, 66:16-19.) Those alpha-amylases have improved thermostability without the need for calcium as an added support at high temperature. (Borchert, Tr. at 26:5-11; '031 patent, 9:48-59, 9:62-66, 10:40-48, 11:41-65.)

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[7]Dr. Thomas Alber is a Professor of Molecular and Cell Biology at the University of California, Berkeley. (Tr. at 199:1-2; Trial Exhibit ["TX"] 532.)

[8]That species has been renamed *Geobacillus stearothermophilus*. (Uncontested Facts, D.I. 101 at ¶ III.S.)

17. Claim 1 of the '031 patent reads:

> A variant of a parent *Bacillus stearothermophilus* alpha-amylase, wherein the variant has an amino acid sequence which has at least 95% homology to the parent *Bacillus stearothermophilus* alpha-amylase and comprises a deletion of amino acids 179 an [sic] 180, using SEQ ID NO:3 for numbering, and wherein the variant has alpha-amylase activity.

('031 patent, 65:11-17.)

18. Claim 3 reads:

> A variant alpha-amylase, wherein the variant has at least 95% homology to SEQ ID NO:3 and comprises a deletion of amino acids 179 and 180, using SEQ ID NO:3 for numbering and wherein the variant has alpha-amylase activity.

(*Id.* at 65:21-66:12.)

19. Claim 5 reads:

> A variant of a *Bacillus stearothermophilus* alpha-amylase, wherein the alpha-amylase variant consists of a deletion of amino acids 179 and 180, using SEQ ID NO:3 for numbering.

(*Id.* at 66:16-19.)

C. *Prosecution History of the '031 Patent*

20. The application that issued as the '031 patent, Application No. 10/025,648 (the "'648 application"), was filed on December 19, 2001. ('031 patent, cover page.) The '648 application was filed as a division of Application No. 09/902,188, filed July 10, 2001, which was a continuation of Application No. 09/354,191, filed July 15, 1999, which was a continuation of Application No. 08/600,656, filed February 13, 1996, which was a continuation of International Application No. PCT/DK96/00056, filed February 5, 1996. (*Id.*) The '648 application claimed priority to a group of four Danish patent applications filed from February 3 to October 6, 1995. (*Id.*) To support an effective

filing date for a United States patent, a foreign priority application must provide a sufficient written description of what is claimed in the United States patent. *In re Gostelli*, 872 F.2d 1008, 1010-11 (Fed. Cir. 1989). The earliest of the four Danish applications that discloses a *Bacillus stearothermophilus* alpha-amylase is the one that was filed on March 29, 1995, Application No. PA 1995 00336. (Trial Exhibit ["TX"] 101, D.I. 121 at A-7955-8035.) Thus, according to Defendants (D.I. 115 at 4-5, ¶¶ 22-23), no earlier Danish application will support an effective filing date for the '031 patent, and the earliest possible effective filing date for that patent is March 29, 1995.[9]

1. *The Original Claims*

21. A preliminary amendment to the '648 application was filed on December 19, 2001. (TX 101, D.I. 121 at A-7045-48.) That amendment canceled claims 1-29 and added 18 new claims, numbered 30-47. (*Id.*) New claims 30-39 were directed to alpha amylases, and claims 40-47 were directed to DNA, vectors, host cells, and methods of expressing the alpha-amylases. (*Id.*)

22. Claim 30 was an independent claim that read:

> A variant of a parent alpha-amylase enzyme, wherein said parent alpha-amylase has an amino acid sequence which has at least 80% homology to SEQ ID NO:3, and wherein said variant comprises deletions at positions equivalent to positions 179 and 180 in SEQ ID NO:3 (using SEQ ID NO:3 for numbering).

(*Id.* at A-7045.)

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[9]While Novozymes does not expressly agree in its proposed findings that March 29, 1995 is the effective filing date, it does not dispute in its opposition to Defendants' invalidity argument that the references raised by Defendants are prior art. (*See* D.I. 125 at 21-22, 24-25.)

23. Claims 31-34 depended directly from claim 30. (*Id.* at A-7045-46.) Claims 31-33 specified the homology between the parent alpha-amylase amino acid sequence and SEQ ID NO:3 as at least 85%, 90%, and 95% respectively. (*Id.* at A-7045.) Claim 34 claimed "[t]he variant of claim 30, wherein the variant further comprises amino acid substitutions of a cysteine at positions equivalent to positions 349 and 428 in SEQ ID NO:3." (*Id.* at A-7046.)

24. Claim 35 was an independent claim that read:

> An isolated alpha-amylase enzyme comprising an amino acid sequence having an amino acid sequence which has at least 80% homology to SEQ ID NO:3, modified by having deletions at positions equivalent to positions 179 and 180 in SEQ ID NO:3.

(*Id.*)

25. Claims 36-39 depended directly from claim 35. (*Id.*) Claim 36 claimed "[t]he alpha-amylase enzyme of claim 35, wherein said alpha-amylase enzyme is further modified by having amino acid substitutions of a cysteine at positions equivalent to 349 and 428 in SEQ ID No:3." (*Id.*) Claims 37-39 specified the homology between the alpha-amylase amino acid sequence and SEQ ID NO:3 as at least 85%, 90%, and 95% respectively. (*Id.*)

2. *The First Office Action*

26. The examiner issued an office action on July 29, 2003. (*Id.* at A-7619-29.) After a restriction requirement, the applicants elected to prosecute claims 30-39. (*Id.* at A-7621, A-7636.)

a. *Written Description and Enablement*

27. The examiner rejected claims 30-34 for failing to meet the written description requirement of 35 U.S.C. § 112. (*Id.* at A-7623.) According to the examiner, the specification only described a few representative species of the genus of enzymes that were included in the scope of claims 30-34. (*Id.*) As written, those claims included variant enzymes "with any number of alterations of the parent enzyme as long as amylase activity is maintained." (*Id.*) Given that scope, the specification failed to sufficiently describe the invention so that a skilled artisan would recognize that the applicants were in possession of the invention. (*Id.*)

28. The examiner also rejected claims 30-34 under 35 U.S.C. § 112, because the specification did not enable one skilled in the art to practice the full scope of the claims. (*Id.* at A-7624-27.) While claims 30-34 required the parent alpha-amylases to have at least 80% homology to SEQ ID NO:3, the variants were not so limited. (*Id.* at A-7624.) The claims covered variants "with any number of alterations of the parent enzyme as long as amylase activity is maintained," and as long as the alterations included the deletions of the two amino acids at positions equivalent to 179 and 180 in SEQ ID NO:3. (*Id.*) Considering the number of possible variants, the unpredictability of the art of protein engineering, and the lack of any detailed instruction as to which regions of the alpha-amylase enzymes could be modified without destroying the alpha-amylase activity, the examiner concluded that the specification did not enable one to make variants with any number of alterations relative to the parent. (*Id.* at A-7625-27.)

29. The examiner noted that the written description and enablement rejections for claims 30-34 would be overcome if claim 30 was amended so that the class of claimed variants were required to have "at least 80% sequence identity to SEQ ID NO:3." (*Id.* at A-7627.)[10]

b. *Obviousness*

30. The examiner rejected claims 30-33, 35, and 37-39 under 35 U.S.C. § 103(a) as obvious in light of two references. (*Id.* at A-7627-28.)

31. The first reference ("the Suzuki reference" or "Suzuki"), titled "Amino Acid Residues Stabilizing a *Bacillus* α-Amylase against Irreversible Thermoinactivation" and authored by Suzuki et al., was published in the Journal of Biological Chemistry in 1989. (TX 115, D.I. 122 at A-8233-38.) Suzuki disclosed alpha-amylases from *Bacillus amyloliquefaciens* that were modified by the deletion of two amino acids at positions 176 and 177. (*Id.* at A-8233, A-8237-38.) Alpha-amylases with those deletions had better thermostability. (*Id.* at A-8237-38.)

32. The second reference ("the Bisgård-Frantzen reference" or "Bisgård-Frantzen") was a patent application, Publication No. WO 95/10603, published April 20, 1995 and titled "Amylase Variants." (TX 177, D.I. 122 at A-8403-507.) Bisgård-Frantzen disclosed that the alpha-amylases of *Bacillus amyloliquefaciens*, *Bacillus stearothermophilus*, and *Bacillus licheniformis* were "highly homologous on the amino

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[10]The examiner also rejected claim 36 as indefinite because it was improperly dependent on claim 35, and she suggested a modification to the claim language that would overcome the rejection. (*Id.* at A-7622.) The applicants responded by cancelling claim 36 and adding the limitation to independent claim 35 (*id.* at A-7634, A-7636), and the rejection was withdrawn (*id.* at A-7719).

acid level." (*Id.* at A-8413-14.) A sequence alignment of those alpha-amylases showed that positions 176 and 177 of the *Bacillus amyloliquefaciens* enzyme corresponds to positions 179 and 180 of the *Bacillus stearothermophilus* enzyme. (*Id.* at A-8415-16.)

33. According to the examiner, "it would have been obvious to one of ordinary skill in the art to introduce the [deletions] disclosed by Suzuki . . . into the corresponding positions [179 and 180] of *Bacillus stearothermophilus* α-amylase," in order to increase its thermostability. (TX 101, D.I. 121 at A-7628.) Because of the similarity between the *Bacillus amyloliquefaciens* and *Bacillus stearothermophilus* alpha-amylases revealed by Bisgård-Frantzen, one of ordinary skill in the art would, the examiner concluded, reasonably expect that the change in the *Bacillus stearothermophilus* alpha-amylase would give similar results as those disclosed by Suzuki for the *Bacillus amyloliquefaciens* alpha-amylase. (*Id.*)

3. *Novozymes's Response*

34. On January 13, 2004, Jason Garbell, an in-house patent attorney for Novozymes (Garbell, Tr. at 4:13-17), sent an e-mail message to a group at Novozymes, including the inventors of the '031 patent, commenting on the examiner's obviousness rejection. (TX 110, D.I. 122 at A-8169-70.) In that e-mail, Mr. Garbell proposed two options for responding to the rejection: "Option 1" was to show by experiment that the claimed deletion in *Bacillus stearothermophilus* alpha-amylase yielded unexpected results, and "Option 2" was to add limitations to the rejected claims such as those in claims 34 and 36, which were not rejected for obviousness. (*Id.* at A-8170.) Mr. Garbell preferred Option 1, because that would not require narrowing the scope of the

claims and would limit the design-around opportunities available to competitors. (*Id.*) Genencor was known to be one of those competitors. (*Id.* at A-8169 (referring to Genencor as GCI); Borchert, Tr. at 355:8-356:15.)

35. Mr. Garbell needed to respond to the office action by January 29, 2004 (TX 110, D.I. 122 at A-8170), and the scientists at Novozymes informed him that the experimental work required for Option 1 could not be completed by then (*id.* at A-8169, A-8171). It was suggested that proceeding with Option 2 would "give time" for carrying out the experiments, which might then support broader claims. (*Id.* at A-8169.)

36. On January 14, 2004, the applicants filed an amendment. (TX 101, D.I. 121 at A-7632-37.) In response to the obviousness rejection, claims 34 and 36 were canceled, and independent claims 30 and 35 were amended to add the limitations of claims 34 and 36, respectively. (*Id.* at A-7634, A-7637.)

37. In response to the written description and enablement rejections, the applicants amended claim 30 to recite that the variant "has at least 80% identity to said parent alpha-amylase." (*Id.* at A-7634, A-7636-37.)

4. *The Second Office Action*

38. The examiner issued another office action on April 6, 2004. (*Id.* at A-7717-27.) The obviousness rejection was withdrawn. (*Id.* at A-7719.)

39. The examiner maintained the rejection of claims 30-33 for failure to meet the written description requirement. (*Id.* at A-7719-21.) Again, the examiner said that the specification described only a few of the many alpha-amylases covered by those claims, so that one skilled in the art could not conclude that the applicants had

possession of the claimed invention. (*Id.* at A-7720-21.) The examiner suggested that the claims be narrowed by requiring the variants to have alpha-amylase activity. (*Id.* at A-7721.)

40. The examiner rejected claims 30-33, 35, and 37 for failure to meet the enablement requirement. (*Id.* at A-7721-26.) While the applicants had stated in their response to the first office action that claim 30 had been amended following the examiner's suggestion (*id.* at A-7636-37), the examiner noted that the applicants "did not in fact amend the claim exactly as suggested" (*id.* at A-7725). Rather than requiring the variant to have at least 80% identity to SEQ ID NO:3, as the examiner had suggested (Finding of Fact ["FF"] ¶ 29), the applicants amended claim 30 to require the variant to have at least 80% identity to the parent alpha-amylase (FF ¶ 37). However, the examiner acknowledged that the amendment was "similar" to her suggestion. (TX 101, D.I. 121 at A-7725.) Still, while the examiner recognized that the scope of claims 30-33 had been narrowed, "upon further reconsideration" she believed that the specification did not enable one of ordinary skill to make variants with at least 80% identity to the parent without undue experimentation. (*Id.*) As in the first office action, the examiner noted the large number of possible variants, the unpredictability of the art, and the lack of guidance about which regions of the alpha-amylases could be modified without losing enzyme activity. (*Id.* at A-7721-26.) Claims 35 and 37, which required the variant to have at least 80% and 85% homology to SEQ ID NO:3, respectively, were also not supported by an enabling disclosure, the examiner concluded. (*Id.*)

41. The examiner noted that the specification was enabling for alpha-amylases "having at least 90% homology to SEQ ID NO:3" and having the claimed modifications. (*Id.* at A-7721.) Thus, claims 38 and 39, which required at least 90% or 95% homology to SEQ ID NO:3, respectively, would be allowable, the examiner indicated, if they were rewritten in independent form. (*Id.* at A-7726.)

5. *Evidence of Unexpected Results*

42. In an interview on September 3, 2004, Mr. Garbell and Dr. Borchert discussed with the examiner the obviousness rejection from the first office action. (*Id.* at A-7798-99.) The examiner stated that she was shown a draft declaration that "appear[ed] to show results sufficiently unexpected to overcome" the previous obviousness rejection. (*Id.* at A-7799.) Those unexpected results were later submitted to the examiner in the form of a declaration under 37 C.F.R. § 1.132, dated September 6, 2004 (the "Borchert Declaration"). (*Id.* at A-7739-56.)

43. The Borchert Declaration described the results of an experiment comparing the thermostability of *Bacillus stearothermophilus* alpha-amylase ("BSG"),[11] with and without deletion of residues[12] 179 and 180, and *Bacillus amyloliquefaciens* alpha-amylase ("BAN"), with and without deletion of residues 176 and 177. (*Id.* at A-7739, ¶ 3.) BAN was the alpha-amylase studied by Suzuki. (FF ¶ 31.)

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[11]While "BSG" was sometimes used at trial to refer to the *Bacillus stearothermophilus* organism (*see, e.g.,* Tr. at 177:22-178:7), I will use the term herein to refer to the alpha-amylase.

[12]A residue is an amino acid that has become part of a peptide chain. *See* Merriam-Webster's Medical Dictionary (2002).

44. Genes for the variants of BSG and BAN with their respective deletions ("BSGdel" and "BANdel" respectively) were constructed by standard methods and the gene sequences were confirmed by DNA sequencing. (TX 101, D.I. 121 at A-7740, ¶ 4.) Cells producing each of the four enzymes, BSG, BSGdel, BAN, and BANdel, were grown under identical conditions, and the alpha-amylases were separated from the cells by centrifugation. (*Id.* at A-7740, ¶ 5.) The alpha-amylase-containing supernatants[13] were diluted in buffer containing 0.1 mM calcium and incubated at 80°C in a PCR machine,[14] and at various times the alpha-amylase activity was measured. (*Id.*) According to the Borchert Declaration, the incubation temperature of 80°C was "the highest temperature where [all four alpha-amylases] could be reliably compared." (*Id.*; *see also* Borchert, Tr. at 686:8-688:17 (describing the calibration experiments to determine the temperature at which all four enzymes would yield reliable measurements).)

45. The alpha-amylase activity of each sample was measured at various times, and the results were reported in tabular form as a percentage residual activity at each time. (TX 101, D.I. 121 at 7741-42, ¶ 6.) BSGdel maintained its activity for the longest period of time: 61% residual activity was measured at 4200 minutes, the last time point of the experiment. (*Id.*)

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[13]The supernatant is the liquid that remains after solids are removed by centrifugation. *See* Merriam-Webster's Medical Dictionary (2002).

[14]PCR is the polymerase chain reaction, a "technique for amplifying DNA sequences," American Heritage Dictionary of the English Language (4th ed. 2000), which uses a machine to heat the samples. The PCR machine was used in the Borchert experiment as a heat source, and not, it appears, for anything related to PCR per se.

46. Four data points were omitted before the data were analyzed. First, two measurements for BSGdel taken at 2881 minutes were omitted by a Novozymes lab technician, Vibeke Holbo, because she noted that the sample used for those measurements had evaporated during incubation. (Holbo,[15] Tr. at 671:3-14; Borchert, Tr. at 384:22-385:2, 412:17-24.) Two other measurements for BSGdel taken at 2940 minutes were omitted by Dr. Borchert, because he noted that the measurements "were extremely far apart" and one showed activity above 130%. (Borchert, Tr. at 386:9-15, 412:25-413:2, 414:8-17.) Dr. Borchert decided that he could not "with any confidence include such measurements in the data analysis." (*Id.* at 414:16-17.)

47. A regression analysis was conducted for each data series, and the half-life for each alpha-amylase, i.e. the time at which the alpha-amylase had half of its original activity (Klibanov,[16] Tr. at 515:18-25), was calculated. (TX 101, D.I. 121 at A-7742, ¶ 7.) The four half-lives were: BAN, 0.9 minutes; BANdel, 9.5 minutes; BSG, 92 minutes; BSGdel, 5775 minutes. (*Id.*) Based on those numbers, Dr. Borchert reported that the deletion of residues 176 and 177 in BAN improved thermostability 11-fold, and the corresponding deletion of residues 179 and 180 in BSG improved thermostability 63-fold. (*Id.*) Thus, the thermostability was improved 5.7 times as much in BSG as in BAN (63/11=5.7). (*Id.*)

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[15]Vibeke Holbo has worked at Novozymes for thirty years, and she worked with Dr. Borchert on the experiments presented in the Borchert Declaration. (Tr. at 665:14-17, 20-22, 668:6-8.)

[16]Dr. Alexander M. Klibanov is a Professor of Chemistry and Bioengineering at the Massachusetts Institute of Technology. (Tr. at 510:12-16.)

48. According to Dr. Borchert, the deletion in BSG "has a pronounced and very surprising effect on the thermal stability." (*Id.* at A-7743, ¶ 9.) "[The] results are statistically significant and very surprising as the effect of the double deletion in BSG is significantly greater than what would have been expected based on the combined teachings of Suzuki . . . in view of Bisgaard-Frantzen . . . ." (*Id.* at A-7743-44, ¶ 9.)

6. *Allowance*

49. After the interview on September 3, the applicants submitted an amendment dated September 6, 2004 (*id.* at A-7733-56) that cancelled all the pending claims and added five new claims, numbered 48-52 (*id.* at A-7734). For claims 48, 50, and 52, the applicants removed the requirement for cysteine substitutions at positions 349 and 428, which had been added in response to the obviousness rejection from the first office action. (*Id.*) According to the applicants, an obviousness rejection based on Suzuki and Bisgård-Frantzen, if it were reasserted by the examiner in response to the broadened claims, would be overcome by the evidence of unexpected results in the Borchert Declaration. (*Id.* at A-7736-37.)

50. In response to the earlier enablement and written description rejections, the applicants drafted claims 48-49 and 50-51 to require the variants to have at least 95% homology to the parent *Bacillus stearothermophilus* alpha-amylase and to SEQ ID NO:3, respectively, and to have alpha-amylase activity. (*Id.* at A-7734-36.) As to the enablement rejection, the applicants noted the examiner's suggestion that the claims would be enabled if they required the variants to have at least 90% homology to SEQ ID NO:3. (*Id.* at A-7735-36; *see* FF ¶ 41.) The applicants argued that the enablement

rejection was "rendered moot by the new claims as the new claims recite a homology of 95%." (TX 101, D.I. 121 at A-7736.)

51. On September 21, 2004, the examiner issued a notice of allowance. (*Id.* at A-7791-97.) In her remarks, the examiner stated that the Borchert Declaration "establishes that the claimed variants exhibit unexpectedly large increases in thermostability when compared to the increases in thermostability obtained for the corresponding mutations taught by Suzuki et al. As such the claimed variants are non-obvious over the prior art." (*Id.* at A-7796.) The examiner made no remarks concerning the written description and enablement rejections. (*Id.*)

52. Claims 48-52, submitted by the applicants on September 6, 2004, correspond to claims 1-5, issued without further amendment as the claims of the '031 patent. (*Compare id.* at A-7734 *with* '031 patent, 65:10-66:19.)

D. *The Machius Reference*

53. Another reference relating to alpha-amylases that was the subject of repeated emphasis during trial is entitled "Crystal Structure of Calcium-depleted *Bacillus licheniformis* α-amylase at 2.2 Å Resolution," and was authored by Machius[17] et al. and published in the Journal of Molecular Biology at least as early as March 13, 1995. (TX 173, D.I. 122 at A-8375-90; "the Machius reference".) The applicants did not disclose the Machius reference to the examiner during prosecution of the '648 application. (Garbell, Tr. at 11:22-12:6, 429:2-6; Borchert, Tr. at 372:7-15.)

[17]This is the same Dr. Machius who testified at trial. *See supra* note 5.

54. That reference reports the three-dimensional structure of a calcium-free form of *Bacillus licheniformis* alpha-amylase ("BLA") as determined using x-ray crystallography. (TX 173, D.I. 122 at A-8376, Abstract.) The Machius reference discusses the thermostability of alpha-amylases, including BAN and BSG, in the context of the three-dimensional structure of BLA. (*Id.* at A-8382-85, A-8387.) First, the reference showed a sequence alignment of BLA, BAN (which the reference referred to as "BAA"), and BSG (which the reference referred to as "BstA"), along with the secondary structure[18] elements of BLA determined from the three-dimensional structure. (*Id.* at A-8383-84, A-8387, Fig. 7.) The Machius reference stated that "[a]ccording to the alignment, the three-dimensional structures of [BAN] and [BSG] can be expected to be very similar to that of BLA." (*Id.* at A-8384.) While the paragraph leading up to that statement pointed to Figure 7 of the article, which included secondary structure information, the prediction about the similarity of three-dimensional structure between the three alpha-amylases is based, according to its own terms, on the sequence similarity shown by the "alignment." (*Id.*; *see also* Machius, Tr. at 465:15-22, 492:17-21 (stating that, based on sequence similarity, it "would be reasonable to expect" similarity in three-dimensional structure).) That sequence similarity was also disclosed by the Bisgård-Frantzen reference. (TX 177, D.I. 122 at A-8413, A-8415-16.)

55. Second, the Machius reference specifically discussed, in the context of the BLA structure, the deletions of amino acids 176 and 177 in BAN disclosed by Suzuki. (TX 173, D.I. 122 at A-8384.) The corresponding two amino acids in BLA are

[18]See *supra* note 6.

shown by Machius's three-dimensional structure to be in a loop on the surface of the protein. (*Id.*) Based on the predicted structural similarity between BLA, BAN, and BSG, the deleted amino acids in BAN and BSG would also be expected to be on surface loops. Because of their position on the surface of the protein, a person having ordinary skill in the art would predict that deleting those amino acids would be less likely to disrupt specific interactions that might vary slightly between BLA, BAN, and BSG. (Machius, Tr. at 774:3-22.) According to the reference, the presence of two extra amino acids on the surface loop "could cause increased mobility of this region and a decreased thermostability of the whole protein." (TX 173, D.I. 122 at A-8384.)[19]

56. The Machius reference does not specifically discuss whether a person having ordinary skill in the art would expect the deletion of residues 179 and 180 in BSG to give improved thermostability, although that conclusion might be drawn from the predicted structural similarity between BSG and BAN. The Machius reference also does not discuss the degree of improvement that might be expected.

E. *Marketing of Spezyme Ethyl*

57. Genencor and EDC began selling the accused product, Spezyme Ethyl, in the United States by April 2004. (Uncontested Facts, D.I. 101 at ¶ III.X.)

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[19]The authors noted that the structure revealed by their experiment was without calcium, which is "required to maintain the structural integrity of α-amylases" (TX 173, D.I. 122 at A-8377), and that the protein had been cleaved between amino acids 189 and 190 (*id.*). Both conditions may have caused the lack of defined structure for amino acids 182 to 192. (Machius, Tr. at 470:23-471:16; TX 177, D.I. 122 at A-8377.) However, those conditions do not affect the conclusion that amino acids 179 and 180 are on a loop. (Machius, Tr. at 471:7-22.) Also, while the atomic coordinates were not disclosed with the Machius reference (TX 173, D.I. 122 at A-8388, Acknowledgments), the description of the structure is sufficient to support that conclusion about amino acids 179 and 180 (Machius, Tr. at 478:18-23, 508:2-14, 776:1-17).

58. Genencor sold other alpha-amylases before Spezyme Ethyl (Crabb,[20] Tr. at 32:12-18), including one product called—in an apparent homage to the Mertz family of "I Love Lucy" fame—Spezyme Fred (*id.* at 35:3-9). None of those products had a sufficient combination of acid tolerance, thermostability, and low cost to be economically viable for use in fuel ethanol production. (*Id.* at 32:19-24.) Some Genencor customers demanded an alpha-amylase that was better suited for fuel ethanol production. (*Id.* at 36:3-22.) Efforts to modify Spezyme Fred did not result in a commercialized product for the fuel ethanol market. (*Id.* at 38:6-39:11.)

59. Since April 2004, sales of Spezyme Ethyl have been considerable. (*See* Uncontested Facts, D.I. 101 at ¶ III.Y.)

F. *Amino Acid Sequences of Spezyme Ethyl and G997*

60. The parties agree on the amino acid sequence of Spezyme Ethyl. (*Id.* at ¶ III.Z.) That sequence is 484 amino acids long, and ends with the following ten amino acids at the C-terminus: VSVWVPRKTT. (*Id.*; TX 125, D.I. 122 at A-8345.)

61. The gene for Spezyme Ethyl was originally engineered from an alpha-amylase gene from *Bacillus stearothermophilus* strain ATCC No. 39,709. (TX 194 at A-8521.) An alpha-amylase produced from that gene, before the gene was modified to produce Spezyme Ethyl, was sold by Genencor as "G997." (Crabb, Tr. at 45:16-19, 46:10-13.) One of Genencor's scientists characterized G997 as a "wild type" *Bacillus stearothermophilus* product (*id.* at 40:1-3), a term that means that it is the product of a

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[20] Dr. W. Douglas Crabb worked on the project at Genencor that led to Spezyme Ethyl. (Tr. at 31:24-32:5.)

gene taken from a naturally occurring organism before any modifications are made (Arnold, Tr. at 137:25-138:7).

62. The parties do not agree on the sequence of G997. Specifically, while Novozymes presented a single sequence for G997, Defendants argue that there is no single, stable sequence for G997. (D.I. 116 at 10-11.) Instead, according to Defendants, G997 is a mixture of proteins, each of which has a different number of amino acids deleted from the C-terminus, a feature that Defendants contend disqualifies G997 from being a "*Bacillus stearothermophilus* alpha-amylase", as that term is used in claims 1 and 5. *See infra* Section III.B.1.

63. The amino acid sequence of G997 presented by Novozymes at trial (TX 199, D.I. 122 at A-8529) was determined using mass spectrometry. (Jorgensen,[21] Tr. at 71:16-21; TX 206, D.I. 122 at A-8537-39.2.) At the trial, questions were raised about the provenance of the G997 sample that was analyzed (*see* Tr. at 74-76), so the parties agreed that a G997 sample would be provided by Genencor at the close of trial (D.I. 112). That sample was analyzed by Dr. Jorgensen using the same protocol he used to determine the sequence presented during the trial (TX 206, D.I. 122 at A-8537-39.2), and its amino acid sequence (TX 226, D.I. 122 at A-8556.1) was the same as that presented at trial (TX 199, D.I. 122 at A-8529). The parties have stipulated that the sequence in the exhibit marked "TX 226" is the only sequence of the only alpha-amylase determined by Novozymes to be present in the G997 sample provided by Genencor. (D.I. 112.) That sequence is 486 amino acids long, and ends with the

[21]Dr. Christian Isak Jorgensen is a chemist who heads the protein characterization group at Novozymes. (Tr. at 54:5-12.)

following ten amino acids at the C-terminus: VSVWVPRKTT. (TX 226, D.I. 122 at A-8556.1)

64. Judy Chang, a research associate at Genencor (Crabb, Tr. at 50:13-18), wrote an analytical report dated April 19, 2004 concerning the sequences of G997, Spezyme Ethyl (which was also referred to in the report as "EBS2"), and another alpha-amylase called Termamyl SC. (TX 161, D.I. 122 at A-8365-74.) Ms. Chang reported a single molecular weight for each of the three proteins, determined by mass spectrometry. (*Id.* at A-8368, Table 2.) The measured molecular weights for all three proteins were less than the "theoretical molecular weight" calculated from the DNA sequence of the respective genes. (*Id.* at A-8368.) The three proteins were then subjected to digest mapping (*id.*), a process that yields fragments whose size depends on the particular amino acid sequence of the proteins (*id.* at A-8366). According to that analysis, "[f]ragments were detected which corresponded to the N-terminus for all three enzymes. However, no fragments within 27-29 residues of the C-terminus were found. A truncation of 27-29 amino acids [from the C-terminus] would be consistent with the molecular weights measured for the intact proteins." (*Id.* at A-8368-69.)

65. Testifying on behalf of Defendants, Dr. Alber stated that he interpreted Ms. Chang's report to show multiple sequences for G997, which had different lengths corresponding to deletions of 27, 28, and 29 amino acids from the C-terminus. (Alber, Tr. at 249:13-17, 280:9-19, 291:12-292:8.) Dr. Alber supported that interpretation by pointing to Ms. Chang's statement about a truncation of "27-29 amino acids" (*id.* at

280:9-19) and her use of the plural, "molecular weights," in the description of her results. (*Id.* at 291:12-292:8.)

66. I conclude that Dr. Alber's interpretation is incorrect. First, Ms. Chang reports only one measured molecular weight for each of the three proteins analyzed, including one for G997. (TX 161, D.I. 122 at A-8368, Table 2.) Dr. Alber speculates that the reported molecular weight in Table 2 of the report must be just one of several measured for G997 (Alber, Tr. at 289:8-15), but there is no specific support for that in the report. Second, the digest mapping experiment found "no fragments within 27-29 residues of the C-terminus" (TX 161, D.I. 122 at A-8368-69), indicating that the location of the truncation could not be more precisely determined. The discussion of a truncation of 27-29 amino acids thus appears to reflect the realities of the experiment, rather than the detection of multiple proteins with different truncations. Third, Ms. Chang's reference to "molecular weights" refers to the weights "measured for the intact proteins," i.e., the three proteins that were analyzed: G997, Spezyme Ethyl, and Termamyl SC. (TX 161, D.I. 122 at A-8368-69.) The statement does not show that multiple weights were measured for G997 alone.

67. Thus, Ms. Chang's report is consistent with the sequence of G997 reported in TX 226, which contains a 29 amino acid deletion at the C-terminus relative to the sequence predicted from the gene. (*Compare* TX 226, D.I. 122 at at A-8556.1 *with* TX 161, D.I. 122 at A-8367, Fig. 1.)

68. Two other sequences were determined by Dr. Jorgensen for alpha-amylases produced from the same source as G997, *Bacillus stearothermophilus* strain